Specification

The abstract of the application has been objected to because the first "sentence" is not complete.

Applicant has hereby amended the abstract to contain a complete first sentence.

In view of the foregoing, Applicant respectfully requests withdrawal of this objection.

The abstract has further been amended to include the phrase "or chemical groups" after "individual atoms" in line 14 in order to more accurately reflect the actual procedure that is carried out during optimal ligand design. as described in the specification on page 16 at lines18-22, lead ligand modification is carried out by replacement, deletion or addition of "chemical groups", examples of which are given. Therefore, Applicant submits that this amendment does not introduce new matter and serves to more accurately reflect the invention.

35 U.S.C. § 102(b) Rejection

Claims 2, 6, 8, and 13 stand rejected as being anticipated by Delisi et al., US 5, 495,423. Examiner states that Delisi et al. teaches a computer assisted method and program for predicting the binding affinity of a ligand to a selected binding site in which the coordinates and identity of atoms from a receptor molecule are input into a computer, as is information for atoms of a selected ligand (amino acid or acids), a model of the two is generated, energy of the complex (a 3D model) is minimized, and a binding affinity of the compound for its binding site predicted from the energy minimized structure.

With respect to claims 2 and 13, Applicant hereby amends claims 2 and 13 to recite that the binding site (target) of those claims is one that is generated by a specific method. The method is recited in original claim 1 of the application, now claim 1 of issued United States patent 6,226,603 B1. Since the method of generating binding targets has been deemed patentable, a method for predicting the binding affinity of a ligand for such a binding target should also be patentable. Applicant notes that in original claim 1, the sites were referred to as "binding targets" rather than "binding sites". The two terms are used interchangeably in the specification, and those of skill in the art would recognize that both terms accurately identify a portion of a molecule to which a substance binds. Applicant has also hereby amended claim 2 to correctly recite "compound" instead of "ligand"

in step a. This is to provide correct antecedent basis for the recitation of "compound" in steps c, d, e and f.

Applicant has further amended claim 2 to eliminate the word "selected" in several places in order to simplify the claim language. The use of "selected" does not serve any purpose since if a compound or molecule in undergoing the method of the claim, it has by necessity been "selected". Further, the phrase "for binding" has been eliminated since if a binding affinity is being determined, the affinity is of course "for binding".

With respect to claims 6-10, Examiner states that DeLisis et al. teach that the method disclosed therein may be "performed with two or more amino acids...and specifically with dipeptides..". This is incorrect.

DeLisi et al. teach a method for computing the conformation and location that a protein fragment will obtain in binding to the active site of a receptor. The protein fragment may be a natural ligand or an artificially designed ligand. In the method, the approximate atomic coordinates of the receptor are assumed to be known (column 5, lines 10-11). In order to carry out the method, the binding site is divided into subvolumes or regions, and ultimately, a "map" of the binding potential of each amino acid of the receptor is determined and displayed in matrix form. (column 5, lines 27-33).

Several variants of the method are described. In one, outlined in column 5 at lines 38-50, different alternative configurations of each amino acid within a subvolume are minimized directly.

In a second variation (that which is cited by Examiner as anticipating the present invention) the method is carried out as follows: The coordinates of the molecule in which the receptor (active site) is located are oriented to a grid. For "each of 20 amino acids" (Applicant assumes that is referred to) the binding site is "scanned" by placing each amino acid, one at a time, in various orientations at each grid point in the receptor molecule (column 5, lines 58-60). Then, either the amino acid-receptor molecule electrostatic interaction (column 5, line 61-62) is calculated, or the more complex procedure of total minimization is carried out (column 5, lines 63-66). In either case, the point is that each of the 20 amino acids (or presumably, a selected subset thereof, e.g. those which occur in a ligand of interest) are individually placed in each grid point and the interaction of each individually placed amino acid with the receptor/binding site amino acids at that grid point is

calculated. Then, those positions for which a given amino acid displays a low energy interaction is considered, and those for which there are also several neighboring positions with similar low energies are selected and ranked. This procedure is also described in claim 1 (column 19, lines 11-17), where it is stated that the binding site is scanned by "placing a [i.e. one] model amino acid at each grid point" and determining the interaction energy between the [i.e. only one] amino acid and the binding site...". The figures of the patent also indicate that a single amino acid is used for this step (Figure 1, step 100; Figure 3c, step 220; Figure 3b, steps 120, 122 and 124 or steps 142, 144 and 146).

Next, it is stated that for a peptide chain which is to be placed in the binding site "two or more amino acids in the peptide which have low-energy positions in the active site are selected as stabilizing residues" (column 6, lines 13-16; Figure 3c, step 230). The selected positions must be consistent with the amino acid location (i.e. primary sequence) within the peptide chain. These stabilizing residues are used as anchor positions for modeling the chain within the binding site: their positions are fixed first, before those of the other residues in the chain, which are then "filled in" with a known program (column 6, lines 18-22). This is described more clearly in claim 2, lines 46-51, which states that a "ligand anchor pair" is selected and the ligand structure is completed by filling in the "loop" between the ligand anchor pair (Figure 3c, step 240). Low energy conformations of the docked ligand are then chosen for the second phase of processing by a second algorithm. A description of the second phase is given in column 6, beginning on line 28, and is outlined in Figures 3d and 3e. Basically, this second phase includes accounting for the charged amino and carboxy termini, and iterative minimization. This is also recited in claim 6 at lines 52-56.

The peptide that is finally docked in a binding site may be potentially of any length. However, the iterative process of establishing the low-energy positions within the binding site is carried out with one amino acid at a time. Contrary to Examiner's assertion, column 6, lines 13-14 does not describe performing the method with peptides comprising two of more amino acids, but rather describes selection and placement of the "ligand anchor pair", after the electrostatic determination (or alternatively, full minimization) using one amino acid at a time. Likewise, example 2 describes docking and minimization of the intact ligand after an "electrostatic prescreen" (column 13, line 20). There is no indication or suggestion that the dipeptides were used to carry out the

electrostatic prescreen. On the contrary, the method was carried out as described throughout the specification, claims and drawings, i.e. with one amino acid at a time, followed by a second phase of minimization of an intact ligand which in the case of example 2 were dipeptides.

In contrast, the method of claim 6 of the present application requires the use of dipeptides. The overall method of which claim 6 is a part is described on page 13, at lines 3-20. The dipeptides originate from a library of 400 "seed" dipeptides and are not based on the sequence of a known ligand, since the goal of the procedure is the *de novo* design of a lead peptide ligand. The dipeptide library includes naturally occurring, non-native and chemically modified amino acids. (In contrast, the method of DeLisi et al. is designed to find the lowest energy conformation of a known or predesigned ligand, and individual amino acids are used. DeLisi is silent regarding non-native and chemically modified amino acids.) A target binding site is selected and a computer program is used to assess the binding site according to its geometry, chemical nature, etc. Based on this initial analysis, seed dipeptides which are likely candidates for "fitting" into the binding site are selected from the library and their binding affinities are calculated as described in claim 6. Applicant notes that in the method outlined in claim 6, there is no step of utilizing one amino acid at a time to interrogate the binding site as is described by DeLisi et al. Rather, a selected dipeptide is docked and minimized, and its binding affinity is computed. The process may be repeated for several candidate dipeptides (claim 7). The seed dipeptides with the highest binding affinities are selected for further processing, as described in claims 8 and 9. Basically, for a peptide with a high binding affinity, a longer polypeptide which includes the dipeptide (e.g. a tripeptide with one additional amino acid) is also docked in the binding target, minimized and the binding energy is computed. For example, 20 different tripeptides comprising the dipeptide and one additional amino acid (at either the amino or carboxy terminus) may be analyzed and those with the highest binding affinity chosen for further processing. In this manner, a multi-residue polypeptide with a high binding affinity for the target site can be built up one amino acid at a time, based on the original seed dipeptide.

Applicant submits that the method outlined in claims 6-10 is thus clearly distinct from that of DeLisi et al., which requires determination of the binding affinity of a single amino acid for a single subvolume of a binding site at a time.

In view of the foregoing, Applicant respectfully requests withdrawal of this rejection.

35 U.S.C. § 103(a) Rejection

Claims 2, 6-10 and 13 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of DeLisi et al. and Shakhnovich et al. The method of DeLisi et al. is discussed in detail above. Shakhnovich et al. describe a method for structure-based drug design, including the calculation of the free energy of binding. The method is described in detail in column 10 beginning at line 5. In the method, a single hydrogen molecule, H_2, is positioned randomly in the binding site of interest. One of the H atoms is randomly selected to by the site of a new bond. A fragment is then randomly selected from a library of fragments and is attached to the randomly selected H atom. The resulting new fragment is oriented to a position of lowest energy, a second H atom is selected as a site for the attachment of yet another fragment, and so on. In this manner, a molecule which binds to the site with favorable binding energy is constructed piecemeal.

With respect to claims 2 and 13 of the present application , they have hereby been amended in a manner that distinguishes them from the prior art, as discussed above.

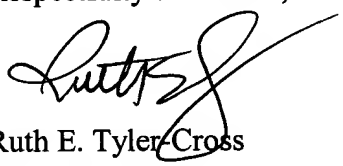
With respect to claims 6-10, Applicant submits that DeLisi et al. as described in detail above do not show or suggest the use of seed dipeptide selection, docking and minimization to grow a peptide chain. The method of Shakhnovich et al. involves the use of an H_2 molecule as the initial "building block", and neither shows or suggests the use of a seed dipeptide for this purpose. The methods of DeLisi et al. and Shakhnovich et al. are independent methods of modeling which it would serve no purpose to combine. Would the H_2 molecule of Shakhnovich et al. be used in addition to or instead of the single amino acid of DeLisi et al.? There is no showing or suggestion in either reference that the methods should or could be combined, and in fact there is no practical way to combine steps of the two methods. Therefore, it cannot be accurately asserted that a combination of DeLisi et al. and Shakhnovich et al. would render the subject matter of claims 6-10 of the present invention obvious.

In view of the foregoing, Applicant respectfully requests withdrawal of this rejection.

Closing Remarks

In view of the above, claims 2, 6-10 and 13 should be deemed new and unobvious over the prior art of record. Reconsideration and allowance of the claims at an early date is requested.

Respectfully submitted,



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